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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/625,847	07/24/2003	Bertrand Pain	37991-0017	8939

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HELLER EHRMAN WHITE & MCAULIFFE LLP
1717 RHODE ISLAND AVE, NW
WASHINGTON, DC 20036-3001

EXAMINER	
KAUSHAL, SUMESH	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 08/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/625,847	PAIN ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-57* is/are pending in the application.

4a) Of the above claim(s) *26-53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25 and 54-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 06/02/06 has been acknowledged.

Election/Restrictions

Applicant's election without traverse of Group I claims 1-25 and 54-57 wherein the elected species are *Non-adherent cells* and *Embryonic stem cells* in the reply filed on 06/02/06 is acknowledged.

Claims 26-53 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 06/02/06.

Claims 9-10 and 14 are objected to because of the following informalities: The instant claims are drawn to a nonelected invention. Appropriate correction is required.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is ***571-273-8300.***

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-25 and 54-57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature Of Invention

The instant invention relates to a method for producing avian cell line.

Breadth Of Claims And Guidance Provided in the Specification

The scope of invention as claimed encompasses method of producing any kind of avian cell line produced by culturing any avian cell in any medium any having any combination of growth factors and any kind of inactivated feeder layer; followed by modification of medium by withdrawing of serum and/or any and all growth factors and/or inactivated feeder layer; followed by isolation of adherent or non-adherent cells lines capable of proliferating in any kind of basal medium in the absence of at least any one of growth factors serum and any kind of inactivated feeder layer.

At best the specification teaches method of producing a chicken embryonic stem cell line using an inactivated "feeder" composed of mouse fibroblasts cell line (STO cells). The specification further teaches that under the initial culture conditions, the presence of growth factors is necessary belonging to two families of factors: the cytokines and the trophic factors. The specification teaches that cytokines are LIF, interleukin 11, interleukin 6, CNTF, oncostatin and cardiotrophin. The specification further states that in a few cases, the combination of a soluble form of the receptors, a for interleukin 6 and CNTF, makes it possible to increase the proliferative effect observed. The specification states that the trophic factors are SCF, IGF-1 and bFGF, which are also used at the start of the culture, as described above. The specification states that their presence is also necessary for obtaining and amplifying the cells. The specification projects that by progressively reducing these growth factors, it is possible to obtain, after a few passages, culture conditions which allow the proliferation of the embryonic or somatic stem cells without the addition of an exogenous growth factor. However the invention as claimed herein does not limit the scope of growth factor and inactivated feeder layer recited in the instant specification. Thus it would require an excessive and undue amount to experimentation to produce an avian cell line using any medium any having any combination of growth factors and any kind of inactivated feeder layer; followed by modification of medium by withdrawing of serum and/or any and all growth factors and/or inactivated feeder layer; followed by isolationof adherent or

non-adherent cells lines capable of proliferating in any kind of basal medium in the absence of at least any one of growth factors serum and any kind of inactivated feeder layer.

State Of Art And Predictability

The state of the art at the time of filing teaches that the production of avian cell line especially the avian embryonic stem cell is highly unpredictable. Pluripotent embryonic stem cells are undifferentiated cells capable of proliferation and self-renewal and have the capacity to differentiate into all somatic cell types and the germ line. Pluripotent stem cells in the chick have been derived from stage X blastoderms and 5.5 day gonadal primordial germ cells (PGCs). The potential to give rise to somatic and germ line chimeras is highly dependent upon the culture conditions and decreases with passage. The answers to fundamental questions regarding segregation of the avian germ line and the molecular basis of pluripotency should foster the full use of avian pluripotent stem cells. The main impetus for the isolation and culture of avian embryonic stem cells has been the hope that such cells could be used to generate transgenic birds with specific modifications to the avian genome.

Cultured blastodermal cells from stage IX–XI chick and stage X–XI quail embryos and reported conditions that allowed for the long-term culture of pluripotent embryonic stem cells. Using alkaline phosphatase as a marker of pluripotency, the best results were obtained with a combination of human LIF, FGF-2, avian or murine SCF, and Il–11 on a feeder layer of inactivated STO fibroblasts. To neutralize any possible induction of differentiation, an antibody against retinoic acid was also added to the media. Like that observed for mouse ESCs, LIF appeared critical to the long-term proliferation and survival of the cultures. In addition, LIF was required to maintain the expression of several markers associated with an embryonic stem cell phenotype, viz. SSEA-1, EMA-1, and EMA-7. Furthermore, telomerase activity was maintained in the avian ESC cultures after multiple passages, but was down-regulated after a pulse of retinoic acid. Furthermore using heterologous and homologous feeder layers and conditioned media containing variety of factors often produce variable results affecting the long term survival of avian embryonic stem cells. For example dissociated cells

from the unincubated chicken blastoderm at stage X were initially cultured with STO feeder layers, primary chick embryonic fibroblast (CEF) feeder layers, or media conditioned by buffalo rat liver (BRL) cells or by the chicken hepatocarcinoma line LMH could not maintain the blastodermal cells beyond two passages. Furthermore when the combination of primary CEFs and media conditioned with the LMH cells were used to culture dispersed cells from the area pellucida of the stage X embryo, the cells very quickly differentiated into the primary fibroblast feeder layer. This was unexpected since both primary CEFs and media conditioned with LMH cells are capable of maintaining mouse embryonic stem cells. Therefore the presence of LIF and retinoic acid critically affect the outcome of any culture conditions in order to produce the chicken embryonic stem cells (see Pettie et al, Mech Dev. 121(9):1159-68. 2004, see pages 1161-1162; Pain et al ,Development. 122(8):2339-48, 1996 see page 2341-2343, ref of record, see US 6,998,266, 2006).

Furthermore it has been suspected that that mammalian cytokines are not fully effective on chicken ES or EG cells given the low identity between chicken and mammalian cytokines. For example, mammalian IL-1 fails to stimulate the division of chicken thymocytes in the presence of submitogenic levels of phytohemagglutinin, and mammalian IL-2 does not induce proliferation of chicken lymphocytes. Therefore, it seemed probable that chicken LIF (chLIF) would be more effective in maintaining chicken ES or EG cells in the undifferentiated state than its mammalian homologue. Chicken LIF has been found indispensable for maintaining the undifferentiated state of chicken blastodermal cells in culture (see Horiuchi et al, J Biol Chem. 279(23):24514-20, 2004). Thus the identification of growth factor used in the context of instant invention is germane in ordered to practice the invention as claimed without further undue amount of experimentation.

Thus considering the state of the art and limited amount of guidance provided in the instant application is it considered highly unpredictable that one skilled in the art would be able to practice the invention as claimed without further excessive and undue amount of experimentation. Furthermore, It is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general

ideas that may or may not be workable (*See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966), Stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."*) Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.

In instant case making any kind of avian cell line produced by culturing any kind of avian cell in any medium having any combination of growth factors, conditions and any kind of inactivated feeder layer; followed by modification of medium by withdrawing of serum and/or any and all growth factors and/or inactivated feeder layer in all possible combinations; followed by isolation of adherent or non-adherent cells lines capable of proliferating in any kind of basal medium in the absence of at least any one of growth factors serum and on any kind of inactivated feeder layer is *not considered routine in the art and without sufficient guidance to a specific culture conditions, growth factors required and feeder layer cells capable of maintaining and promoting avian embryonic stem cell cycling, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.* See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore considering the state of the art and limited amount of guidance provided in the instant specification, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Claim 1-25 and 54-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, sec b) recites "withdrawal of factors". It is unclear what factors are withdrawn in this context.

Claim 57 is indefinite because it is unclear what is the therapeutic protein in this context. For example it is unclear whether the protein is endogenous or the result of exogenous modification of the cells.

Claim 25 is indefinite because it is unclear how a gradual withdrawal of feeder layer is achieved in this context.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 7-13, 15-16, 18-20, 23, 25 and 54-57 are rejected under 35 U.S.C. 102(b) as being anticipated by Pain et al (Development. 122(8):2339-48, 1996 ref. of record).

The cited art teaches a method for producing an avian cell line (CEC) by culturing the chicken embryonic cells on mitomycin C or irradiated STO feeder cells (inactivated) in the presence of LIF, IL-6, IL-11, CNTF and bFGF (page 2340-2343). The cited art further teaches CEC cultures in the presence or absence of LIF (page 2343, fig-4). In addition the cited art teaches a process of making an embryoid bodies (EB) in-vitro by generating non-adherent cells in the absence of LIF, wherein the EB are capable of differentiating into various lineages in non-tissue culture dishes and in the absence of LIF (page 2444, col.1 para. 3-4). The cited art further teaches expression of endogenous alkaline phosphatase activity, telomerase activity and expression of SSEA-1, SSEA-3 and EMA-1 expression (page 340 col.2 page 2342, fig-1, page 2343, fig-3). The cited art further teaches that SSEA-1 and EMA-1 positive cells could be maintained

for at least 35 passages i.e. more than 160 days (page 2343, col.2). Thus give the broadest reasonable interpretation the cited art clearly anticipate the invention as claimed.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to **571-272-0547.** For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**

SUMESH KAUSHAL
PRIMARY EXAMINER
ART UNIT 1633